Handbook of Pharmaceutical Excipients

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Handbook of PHARMACEUTICAL EXCIPIENTS

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Carboxymethylcellulose Sodium

1. Nonproprietary Names

BP: Carmellose sodium
PhEur: Carboxymethylcellulosum natricum
USP: Carboxymethylcellulose sodium

2. Synonyms

Akucell; *Blanose*; *Cekol*; cellulose gum; CMC sodium; *Courlose*; E466; *Nymcel*; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; *Tylose CB*.

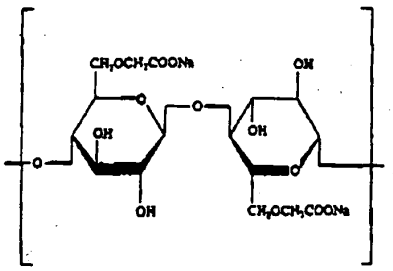
3. Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

4. Empirical Formula Molecular Weight

The USP XXII describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000-700 000.

5. Structural Formula



Structure shown with a degree of substitution (DS) of 1.0.

6. Functional Category

Coating agent; tablet and capsule disintegrant; tablet binder; stabilizing agent; suspending agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.[1] Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant,[2-4] and to stabilize emulsions.[5]

Higher concentrations, usually 4-6%, of the medium viscosity grade is used to produce gels which can be used as the base for applications and pastes; glycerin is often included in such gels to prevent drying out. Carboxymethylcellulose sodium is additionally one of the main ingredients of self adhesive ostomy, wound care and dermatological patches where it is used to absorb wound exudate or transepidermal water and sweat.

Carboxymethylcellulose sodium is also used in cosmetics, toiletries[6] and food products.

Use	Concentration (%)
Emulsifying agent	0.25-1.0
Gel-forming agent	4.0-6.0
Injections	0.05-0.75
Oral solutions	0.1-1.0
Tablet binder	1.0-6.0

8. Description

Carboxymethylcellulose sodium occurs as a white to almost white colored, odorless, granular powder. *See also* Section 19.

9. Pharmacopeial Specifications

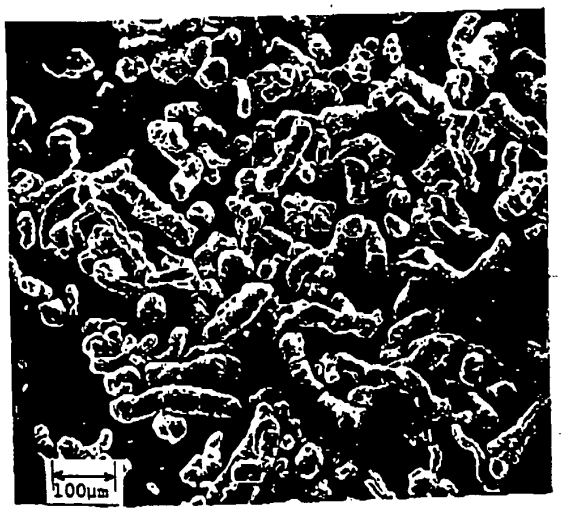
Test	PhEur 1986	USP XXII (Suppl 8)
Identification	+	+
pH (1% w/v solution)	6.0-8.0	6.5-8.5
Appearance of solution	+	—
Viscosity	+	+
Loss on drying	≤ 10.0%	≤ 10.0%
Heavy metals	≤ 20 ppm	≤ 0.004%
Chloride	≤ 0.25%	—
Sodium glycolate	≤ 0.4%	—
Sulfated ash	20.0-33.3%	—
Assay (of sodium)	6.5-10.8%	6.5-9.5%

SEM: 1
Excipient: Carboxymethylcellulose sodium
Manufacturer: Buckeye Cellulose Corp
Lot No.: 9247 AP
Magnification: 120x
Voltage: 10 kV

SEM: 2
Excipient: Carboxymethylcellulose sodium
Manufacturer: Buckeye Cellulose Corp
Lot No.: 9247 AP
Magnification: 600x
Voltage: 10 kV

SEM: 4
Excipient: Carboxymethylcellulose sodium
Manufacturer: Hercules Ltd
Lot No.: 21 A-1 (44390)
Magnification: 600x
Voltage: 20 kV

SEM: 3
Excipient: Carboxymethylcellulose sodium
Manufacturer: Hercules Ltd
Lot No.: 21 A-1 (44390)
Magnification: 120x
Voltage: 20 kV



10. Typical Properties

Density (bulk): 0.75 g/cm^3
Dissociation constant: pK_a = 4.30
Melting point: browns at approximately 227°C, chars at approximately 252°C.
Moisture content: typically, contains less than 10% of water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37°C at relative humidities of about 80%. *See also* HPE Data and Section 11.
Solubility: practically insoluble in acetone, ethanol, ether and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS). *See* Section 19.
Viscosity: various grades of carboxymethylcellulose sodium are commercially available which have differing aqueous viscosities; aqueous 1% w/v solutions with viscosities of 5-4000 mPa s (5-4000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity.[6] Viscosities of various grades of carboxymethylcellulose sodium are shown in Table I. *See also* Section 11.

Table I: Viscosity of aqueous carboxymethylcellulose sodium solutions at 25°C.

Grade	Concentration (% w/v)	Viscosity (mPa s)
Low viscosity	4	50-200
Medium viscosity	2	400-800
High viscosity	1	1500-3000

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content	MC-10	10	8.5%
Moisture content	MC-7	5	6.5%
Moisture content	EMC-1	10	*See* Fig. 1.

Supplier: Hercules Ltd (Lot #76493).

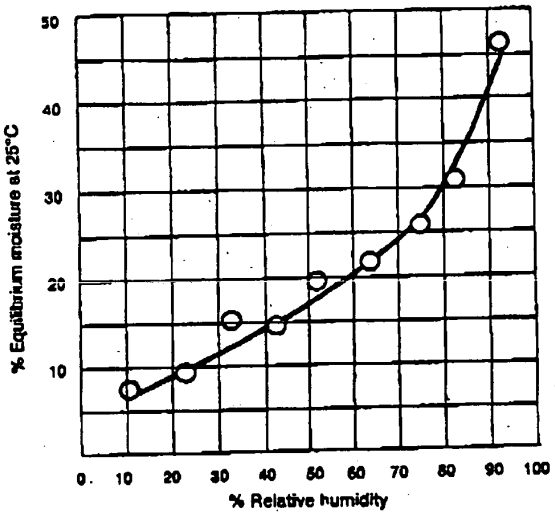


Fig. 1: Equilibrium moisture content of carboxymethylcellulose sodium.

11. Stability and Storage Conditions

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under high humidity conditions carboxymethylcellulose sodium can absorb a large quantity (> 50%) of water. In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time.[7]

Aqueous solutions are stable between pH 2-10; below pH 2 precipitation can occur while above pH 10 solution viscosity rapidly decreases. Generally, solutions exhibit maximum viscosity and stability at pH 7-9.

Carboxymethylcellulose sodium may be sterilized in the dry state by maintaining it at a temperature of 160°C for 1 hour. However, this process results in a significant decrease in viscosity and some deterioration in the properties of solutions prepared from the sterilized material.

Aqueous solutions may similarly be sterilized by heating although this also results in some reduction in viscosity. After autoclaving, viscosity is reduced by about 25% although this reduction is less marked than for solutions prepared from material sterilized in the dry state. The extent of the reduction is dependent on the molecular weight and degree of substitution; higher molecular weight grades generally undergo a greater percentage reduction in viscosity. Sterilization of solutions by gamma irradiation also results in a reduction in viscosity.

Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative.[8]

The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts f iron and some other metals, such as aluminum, mercury and zinc; it is also incompatible with xanthan gum. Precipitation can occur at pH < 2 and when mixed with ethanol (95%).

Carboxymethylcellulose sodium also forms complex coacervates with gelatin and pectin. It additionally forms a complex with collagen and is capable of precipitating certain positively charged proteins.

13. Method of Manufacture

Alkali cellulose is prepared by steeping cellulose obtained from wood pulp or cotton fibres in sodium hydroxide solution. The alkali cellulose is then reacted with sodium monochloroacetate to produce carboxymethylcellulose sodium. Sodium chloride and sodium glycolate are obtained as by-products of this etherification.

14. Safety

Carboxymethylcellulose sodium is used in oral, topical and some parenteral formulations. It is also widely used in cosmetics, toiletries and food products and is generally regarded as a nontoxic and nonirritant material. However, oral consumption of large amounts of carboxymethylcellulose sodium can have a laxative effect; therapeutically 4-10 g, in daily divided doses, of the medium and high viscosity grades of carboxymethylcellulose sodium have been used as bulk laxatives.

The WHO has not specified an acceptable daily intake for carboxymethylcellulose sodium as a food additive since the levels necessary to achieve a desired effect were not considered to be a hazard to health.[9]

In animal studies, subcutaneous administration of carboxymethylcellulose sodium has been found to cause inflammation and in some cases of repeated injection fibrosarcomas have been found at the injection site.[10]

Hypersensitivity and anaphylactic reactions have occurred in cattle and horses which have been attributed to carboxymethylcellulose sodium in parenteral formulations such as vaccines and penicillins.[11,12]

LD_{50} (guinea pig, oral): 16 g/kg[13]
LD_{50} (mouse, oral): > 27 g/kg
LD_{50} (rabbit, oral): > 27 g/kg
LD_{50} (rat, oral): 27 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Carboxymethylcellulose sodium may be irritant to the eyes. Eye protection is recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations, inhalations, intra-articular, intrabursal, intradermal, intralesional, IM, intrasynovial and SC injections, oral capsules, drops, solutions, suspensions, syrups and tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Braz. Cz, Egypt, Eur, Fr. Gr, Hung, Ind, It, Jpn, Mex, Neth, Nord, Rom, Swiss, US and Yug.

18. Related Substances

Carboxymethylcellulose Calcium; Carboxymethylcellulose sodium 12; Croscarmellose Sodium.

Carboxymethylcellulose sodium 12

Pharmacopeias: USPNF.

Comments: carboxymethylcellulose sodium 12 is the sodium salt of a polycarboxymethyl ether of cellulose. Its degree of substitution is between 1.15-1.45, corresponding to a sodium content, calculated on the dry basis, of 10.5-12.0%.

19. Comments

A number of grades of carboxymethylcellulose sodium are commercially available, the most frequently used grade having a degree of substitution (DS) of 0.7. The DS is defined as the average number of hydroxyl groups substituted per anhydroglucose unit and it is this which determines the aqueous solubility of the polymer.

Grades are typically classified as being either low, medium or high viscosity. The degree of substitution and the maximum viscosity of an aqueous solution of stated concentration should be indicated on any carboxymethylcellulose sodium labelling. Carboxymethylcellulose sodium has been reported to give false positive results in the LAL test for eudotoxins.[14]

20. Specific References

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